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Significance of Host Defence Genetics Initiative in Pneumonia

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Abstract

Pneumonia, a prevalent and life-threatening respiratory infection, continues to pose a significant global health challenge. This article provides a comprehensive review of recent advances in understanding the host defence mechanism of pneumonia. The genetic interaction between innate and adaptive immunity plays a vital role in the functioning of the human immune system. The range of genetic markers that influence an individual's response to the infection is one of the primary elements adding to the complexity of pneumonia. One of the most crucial things to consider when examining the genetics of immune activation is the signalling mechanisms initiating immunological responses. GWAS includes extensive analyses of DNA variations across the whole genome, allowing for the identification of genetic loci and potentially causative genes. Understanding the interactions between these genetic characteristics and the host's immune system is necessary to develop effective treatment approaches. Integrating genetic information with other characteristics, such as microbiological and environmental factors, is a crucial area of focus in pneumonia research. Advanced gene editing and therapeutic techniques have promising futures in pneumonia genetic research.

Keywords: Pneumonia, streptococcus pneumoniae, pneumococcal disease, genetic diseases

Introduction

Hippocrates initially characterized pneumonia (Karetzky et al., 1993) (460–370 BC). Twenty-two decades later, in 1819, Laennec first described its clinical and pathological aspects (Mercier, 2014). Rokitansky, in 1842, was the first to distinguish between lobar and bronchopneumonia (Zinserling and Zinserling, 2021). At least 28 phrases were employed to diagnose pneumonia during the ensuing 47 years, and by 1929, there were 94 terms in total—12 sub-terms—listed in the Manual of the International List of Causes of Death (Ayegbayo, 2018).

Depending on whether you approach the condition from a pathological, radiological, microbiological, or clinical perspective, the precise description of pneumonia is complex (O'Grady et al., 2014). Long-held beliefs about pneumonia, particularly community-acquired pneumonia (CAP), have also been called into doubt by recent radiological and clinical studies, which have also questioned the radiological "gold standard" of a chest radiograph (Berg et al., 2022).

Although pneumonia is the leading cause of severe illness and mortality in children under the age of five globally, doctors have limited ability to infer an infectious pathological process in the lung from particular aspects of the history and examination (Wardlaw et al., 2006). Differentiating between pneumonia and many familiar children's diseases, such as malaria, bacterial sepsis, and severe anaemia, can be tricky since they have many clinical symptoms and indications (Scott et al., 2012).

Around the world, pneumonia is a prevalent cause of adult morbidity and mortality (McAllister et al., 2019). However, most research that has helped us understand pneumonia comes from wealthy Western nations (Madhi et al., 2013). The disease's epidemiology, the range of causative microorganisms, and essential prognostic variables are all well-characterized in these contexts, and national management guidelines standardize the

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clinical care approach (Martinez-Garcia et al., 2020). The diagnosis of pneumonia in adults is mainly based on distinctive radiographic alterations in the chest (Franquet, 2001). However, a chest radiograph performed at the beginning of the disease often shows no abnormalities; also, radiological facilities are not always available in developing countries. Many children with suggestive clinical indications of pneumonia and who respond to proper medications do not exhibit any abnormalities on the chest radiograph(Den Boon et al., 2005). In summary, there is not a single, widely applicable definition of pneumonia in children that is sensitive, precise, and consistent.

Host Defence Mechanism

In a world full of microbes, a multicellular organism's existence depends on a network of defence mechanisms called host defence mechanisms that involve multiple layers of interacting systems (Ulvestad, 2009). Pathogenic bacteria typically make their first contact with their host either inside or outside of the body. Microorganisms are primarily introduced and deposited on the surface of the airways, primarily by inspired air (Hakansson et al., 2018).

Genetic Factors in Immune Response

Several different genetic controls must be involved in the intricate process of the immune system's reaction to a particular antigen (Mcdevitt and Benacerraf, 1969). After being introduced into the animal, the antigen must interact with one, and most likely several, cell types (Siskind and Benacerraf, 1969). This will start a complicated process of cell division and differentiation that will eventually lead to the appearance of sensitized lymphoid cells that can specifically interact with the antigen and plasma cells that produce specific antibodies against the antigen (Kato et al., 2013). Although not every stage of this process is understood, it is evident that genetic control might be used in various ways.

The Genetic Basis of Innate Immunity in Pneumonia

The lung's first line of defence is the airway epithelium. In addition to producing chemokines and cytokines like IL-6, CXCL8, IL-1β, GM-CSF, and G-CSF that attract and activate phagocytic cells to destroy organisms and infected cells, airway epithelial cells serve as a mechanical barrier to prevent infection (Parker and Prince, 2011). Encounters with microbes usually trigger an inflammatory response because the lung is ordinarily sterile. This response may arise from the organism's direct cytopathic effects or the host's reaction to these organisms(Wilson and Wilson, 2021).

Many natural antibacterial substances, including cationic defensins and larger proteins like lysozyme, are present in the airway fluid (Rogan et al., 2006). Apart from the antimicrobial proteins present, the airway epithelium expresses a variety of sensors that are used to identify pathogens. Intact bacteria, viruses, fungi, or, more frequently, the parts of these organisms that shed and attach themselves to surface or intracellular receptors can all trigger immune signals(Wilson and Wilson, 2021). Pathogen-associated molecular patterns (PAMPs), which include shed components like LPS and flagella, can penetrate the respiratory mucus layer and bind to epithelial receptors that trigger inflammation even without direct epithelial contact (Gómez and Prince, 2008). The majority of the innate immune system perceives is the identification of PAMPs. By quickly regulating secondary effects linked to neutrophils and their products and effectively eliminating detected pathogens, the mucosal response—particularly the innate response—maintains the sterility of the lower airways (Bartlett et al., 2008).

Controlling the duration and intensity of the proinflammatory signalling that is started in the airway is essential (Hewson et al., 2005). Excessive inflammation (acute pneumonia) is linked to respiratory impairment and needs to be closely managed, possibly more so than at any other location (Steel et al., 2013). Therefore, activation of the innate immune system's regulatory components, including activator protein 1, IFN regulatory factors (IRFs), NF-κB, and mitogen-activated protein kinases (MAPKs), is a key component of mucosal immunity (Jobin and Sartor, 2000).

Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) are recognized by these Pattern Recognition Receptors (PRRs) Genes (Cicchinelli et al., 2024). Examples include Toll-like receptors (TLRs), nucleotide-binding oligomerization domain-like receptors (NLRs), and retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs) are among the genes implicated in the innate immune response to pneumonia (Martinez et al., 2017). TLRs initiate an immune response when they identify particular patterns in pathogens, such as viral nucleic acids and bacterial lipopolysaccharides. In addition to

identifying pathogen-associated molecular patterns, NLRs and RLRs also start the inflammatory cytokine production process (Le et al., 2023).

Complement System Genes generate proteins that are part of the complement system; this aid in the defence of injured cells and micro-organisms such as bacteria by antibodies and phagocytic cells. For instance, C1QA, C1QB, and C1QC genes encode smaller parts of the C1 complex that play a pivotal role in complement activation throughout the pathway. C3 and C5 genes code for vital proteins involved in complement activation and membrane assault complex assembly (Alrashidi, 2016, Ricklin et al., 2016, Zhang et al., 2013).

The Genetic Basis of Adaptive Immunity in Pneumonia

The body uses adaptive immunity as an essential defence mechanism to combat many infections, including bacteria that can cause pneumonia (Eisele and Anderson, 2011). The intricate interaction of genetic variables that control this complex immune system is crucial in determining the nature of the immunological response (Brodin and Davis, 2017). This effective defence system depends on mounting targeted, long-lasting immune responses and identifying and eliminating foreign invaders (Baumgarth et al., 2005).

B cells are specialized cells that produce antibodies, which is how humoral immunity, often called antibody-mediated immunity, is achieved (Rijkers and Meek, 2019). An individual's genetic composition influences the quantity and kind of antibodies produced in response to pneumonia (Zhang et al., 2022). Various antibody variants are produced due to rearrangements in the genes that produce antibodies. Due to this genetic shuffle, the immune system can identify multiple antigens found in bacteria that cause pneumonia (Leist and Baric, 2018).

Moreover, humoral responses are strongly influenced by rearrangements in the B-cell receptor gene. B cells develop unique antigen receptor specificity through genetic recombination, allowing them to identify and neutralise certain infections. Because of this genetic diversity, the immune system may produce specialized antibodies to battle agents that cause pneumonia (Rawlings et al., 2012).

T cells are necessary to invade the body's cells by pathogens for cell-mediated immunity to take effect (Broere and van Eden, 2019). Genetic factors also affect the diversity and specificity of T-cell receptors (TCRs). Like B-cell receptors, TCRs are encoded by genes that undergo genomic rearrangement (Hodges et al., 2003). The diversity and specificity of TCRs are influenced by genetic changes, which can impact an individual's vulnerability to pneumonia and the efficiency of their immune response (Roux et al., 2023). The course of cell-mediated immunity can also be affected by variations in the genes that code for cytokines and their receptors, which are crucial for T-cell activation and proliferation (Broere and van Eden, 2019).

Genetic polymorphisms in genes coding for cytokines and their receptors also affect the adequacy of cell-mediated immune response against pneumonia (Smatti et al., 2022). Genetic differences in these genes can affect the generation and activity of cytokine signalling molecules that control immune cell function (Turner et al., 2014). Consequently, the immunological response to pneumonia is impacted since cytokines regulate multiple immune mechanisms, such as immune cell recruitment and inflammation (Bordon et al., 2013).

Major Histocompatibility Complex (MHC) genes are also necessary for T-cell activation and antigen presentation, among other genes associated with adaptive immunity. MHC molecules present antigenic peptides to T lymphocytes, allowing them to detect and eradicate infected cells. The acquired immune system utilizes MHC genes for identifying foreign particles due to the genes encoding cell-surface proteins (Singh et al., 2010). In this regard, the MHC proteins' human leukocyte antigen (HLA) genes, which comprise HLA-A, HLA-B, and HLA-DR, must exist for the presentation of antigens (Spínola, 2016). Furthermore, genes that make antibodies, such as immunoglobulin genes, TCR alpha, beta TCR genes, cytokine receptor genes, etc., can produce antibodies that can kill pathogens and help remove them (Varadé et al., 2021).

The formation of B-cell receptors depends on immunoglobulin genes, which include the heavy chain IgH, the kappa light chain IgK, and the lambda light chain IgL. IgH, IgK, and IgL encode the heavy and light chains of immunoglobulins assembled upon B-cell receptors (Bruzeau et al., 2022). For TCR alpha and Beta TCR genes, the genes encoding the alpha and beta chains play a role in T-cell receptor construction, which is essential to T-cell activity. These genes tailor the T-cell receptor, enabling it to distinguish between antigens more specifically (Rego et al., 2019). Cytokine receptor genes are crucial for lymphocyte growth and development, differentiation, and activation. These genes are significant for regulating immunological responses

because they generate receptors that are highly reactive to cytokines, which in turn control the ultimate fate and functionality of lymphocytes within the intricate immune system network, e.g., IL2RA and IL2RB, which encode the interleukin-2 receptor alpha and beta subunits for T cell proliferation (Druszczyńska et al., 2022).

Genetic Influence on the Interplay between Innate and Adaptive Immunity

The genetic interplay between innate and adaptive immunity plays a critical role in the functioning of the human immune system (Kumar, 2020). Genetic differences affect the immune activation signalling pathways, affecting how well innate and adaptive responses coordinate (Holgate, 2012). HLA genes are crucial in this genetic regulation. A class of genes known as HLA genes encodes the proteins T cells use to display antigens and identify infections (Crux and Elahi, 2017). For an immune response to be mounted effectively, this procedure is essential. These HLA genes' genetic changes may result in variances in the capacity to identify and present antigens, which may impact the immune system as a whole (Gutierrez-Arcelus et al., 2016).

The signalling pathways that trigger immunological responses are among the most important factors to consider when investigating the genetics of immune activation (Hu and Ivashkiv, 2009). Numerous genes tightly regulate these pathways, whose changes can significantly impact immunological activation. Genetic differences can affect the duration and strength of immune responses by altering downstream signalling molecules and receptor expression (Wells et al., 2003). Genetic variants can cause various effects, such as hyperactive immune responses that can lead to autoimmunity, chronic inflammation or weakened immunological responses that make people more susceptible to infections (Manthiram et al., 2017). Thus, preserving a fine balance between avoiding inflammatory illnesses and an efficient immune response depends critically on the genetic regulation of immune signalling pathways (Devenish et al., 2021).

Host Susceptibility and Resistance to Pneumonia

One of the main factors contributing to the complexity of pneumonia is the variety of genetic markers that affect how an individual reacts to the infection (Dallaire et al., 2001). Genes linked to pneumonia susceptibility and host resistance have been thoroughly studied (Malo and Skamene, 1994). The observed diversity in illness progression and severity can be attributed to genetic polymorphisms in important genes (Kinane and Hart, 2003). The TLR family of genes is one of the notable examples; these genes are essential for identifying infections and starting an immune response. TLR gene polymorphisms are possible indicators of pneumonia resistance or susceptibility (Chatzi et al., 2018).

Furthermore, some genes involved in the inflammatory response have been implicated in pneumonia risk (Kumar, 2020). Evidence links polymorphisms in the interleukin-1 (IL-1) family genes, such as IL-1β and IL-1RN, to altered cytokine production and an increased risk of pneumonia. These variations might knock off the equilibrium between the body's pro- and anti-inflammatory reactions, which could result in insufficient pathogen clearance (Chiche et al., 2001).

Gene-Wide Association Studies (GWAS)

Several studies have effectively found new genes and pathways linked to resistance and susceptibility to pneumonia. Large-scale investigations of DNA variations throughout the entire genome are included in GWAS, which makes it possible to identify genetic loci and perhaps causal genes (Rautanen et al., 2015). New GWAS research has illuminated important genes and networks linked to pneumonia. For example, genes involved in the cilia structure and function, such as DNAH8 and ARMC4, have been implicated in susceptibility to respiratory infections, including pneumonia. These results underline ciliary activity's role in pathogen clearance and point to possible treatment targets (Legendre et al., 2021).

Challenges and Future Perspectives

The intricate genetic architecture of host defences poses formidable obstacles to the field of pneumonia-related genetics investigation (Shah et al., 2018). As a complex infectious disease, pneumonia is impacted by several hereditary variables (Menendez et al., 2004). Creating successful treatment plans requires understanding how these genetic variables interact with the host's immune system.

Another important area of attention in pneumonia research is integrating genetic data with other parameters, including microbial and environmental factors. The combination of environmental exposures and genetic predisposition can greatly influence pneumonia susceptibility. Researchers can create individualised treatment plans and develop a

more thorough understanding of the condition by combining data from several sources (Gjini, 2017).

Pneumonia genetic research has bright futures for sophisticated gene editing and therapeutic approaches. Recent developments in genetic engineering, including the CRISPR-Cas9 system, open up new possibilities for precise gene editing. By strengthening the host's immune response or going straight after the infectious agent, these methods have the potential to change the way pneumonia is treated completely (Kishnani et al., 2012).

Conclusion

The study concluded that pneumonia is highly prevalent worldwide in the age group under five. The infectious pathological material inhibits the lungs first contact with their host either inside or outside of the body. The limited identification is due to the illness's complexity, combining genetic predisposition and environmental exposure. Innate and adaptive immune responses are involved in the intricate and diverse host defence mechanisms against pneumonia. Pneumonia risk has been demonstrated to be influenced by polymorphisms in immune response-related genes, including those encoding cytokines, TLR, and other immune system components. More understanding of the genetic underpinnings of the host's defence against pneumonia is anticipated through future genomics and personalized medicine research, opening the door to more specialized treatments and better patient outcomes.

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